Identification of Androgen Receptor Splice Variants in the Pten Deficient Murine Prostate Cancer Model.

Journal: PLoS One

Publication Year: 2015

Authors: Mengmeng Liang, Helty Adisetiyo, Xiuqing Liu, Ren Liu, Parkash Gill, Pradip Roy-Burman, Jeremy O Jones, David J Mulholland

PubMed link: 26196517

Funding Grants: CIRM Stem Cell Biology Training Program

Public Summary:
Findings presented here provide evidence for the presence of novel variants detectable in the primary organ system of genetically engineered Pten null mice highlighted by the enhanced variant expression during progression at castrate androgen levels.

Scientific Abstract:
Androgen receptor (AR) variants are associated with resistance to anti androgen therapy both in human prostate cancer cell lines and clinical samples. These observations support the hypothesis that AR isoform accumulation is a consequence of selective therapeutic pressure on the full length AR. The Pten deficient prostate cancer model proceeds with well-defined kinetics including progression to castration resistant prostate cancer (CRPC). While surgical castration and enzalutamide treatments yield an initial therapeutic response, Pten-/-epithelia continue to proliferate yielding locally invasive primary tumor pathology. That most epithelium remains AR positive, but ligand independent, suggests the presence of oncogenic AR variants. To address this hypothesis, we have used a panel of recently described Pten-/- tumor cell lines derived from both from hormone intact (E4, E8) and castrated Pten mutants (cE1, cE2) followed by RACE PCR to identify and characterize three novel truncated, amino terminus containing AR variants (mAR-Va, b, c). Variants appear not only conserved throughout progression but are correlated with nearly complete loss of full length AR (AR-FL) at castrate androgen levels. The overexpression of variants leads to enhanced transcriptional activity of AR while knock down studies show reduced transcriptional output. Collectively, the identification of truncated AR variants in the conditional PTEN deletion model supports a role for maintaining the CRPC phenotype and provides further therapeutic applications of this preclinical model.